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(54) Title: PROCESS FOR PREPARING MICROEMULSION

(57) Abstract

Microemulsions of fatty oils in water are prepared by heating a crude emulsion of these ingredients to above the phase inversion temperature and then cooling to room temperature. The emulsions are useful for drug delivery.

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PROCESS FOR PREPARING MICROEMULSION

Cross Reference to Related Application

This application is related to United States Serial No. 375,556, filed July 5, 1989.

Background of the Invention

This invention relates to the preparation of microemulsions for pharmaceutical applications in which an oil such as a triglyceride is dispersed in an aqueous phase with the aid of emulsifiers. The emulsions are useful as drug carriers.

Microemulsions display indicia of inherent stability and behave as solutions, i.e., as a single phase. They are well known in the enhanced oil recovery art and have achieved some recognition in medical applications. See, e.g., U.S. 3,989,843 to Pierre Chabert et al. Such emulsions can be formed with relatively mild agitation and are stable for months over a specified temperature range. Ideally, the range of temperature stability encompasses the intended use which, for internal medical application, is about 18-43°C., i.e., from slightly below room temperature to the temperature of a high fever.

Some workers use the term micro in microemulsion as designating a very small particle size. While this is in accord with the general definition of the term micro, more recently, microemulsion has come to refer to emulsions whose ease of preparation indicates an inherent stability

and whose long-term stability goes well beyond that displayed by ordinary emulsions, even those of very small particle size. Along these lines, it will usually be found that where the micro descriptor refers merely to particle size, the emulsion is made with homogenizers, fluidizers or other high shear procedures which are characteristically unnecessary with "true" microemulsions. See, for example, European Patent Application 0211258.

The advantages of microemulsions are well known. Their indefinite shelf life adds to the useful life of the product and the small particle size allows them to reach parts of the body larger particles would not. This latter aspect is particularly important when an emulsion is used to carry drugs, as opposed to, say, nutrients, since localized delivery of the drug is often essential to receiving its optimum therapeutic value.

Summary of the Invention

My invention is an improved process for forming a microemulsion which involves heating a coarse emulsion of the ingredients at above a critical temperature, the phase inversion temperature (PIT), to "break" this coarse emulsion into two phases and then cooling to below the PIT with gentle mixing until the microemulsion forms. This passage through the PIT results in a smaller particle size emulsion of greater stability than is obtained by conventional mixing methods. My emulsions not only have a very small particle size but they are dilutable, without breaking, with water and normal biological fluids. It is also important that my composition contain one high molecular weight surfactant having a molecular weight greater than 2000 and that it be dissolved in the oil when the coarse emulsion is formed.

Prior Art

It is known to emulsify fatty oils with the ingredients used in my invention. However, I believe I am

the first to obtain a microemulsion of fatty oils by using the preparative method disclosed herein and without the use of high-energy mixing devices. Although emulsions have been heated in the course of their preparation (see, e.g., U.S. 4,857,335), there is no recognition of the need to break an initial emulsion and then reform it in order to obtain a microemulsion.

Detailed Description of Invention

Each component of my composition is described below.

The oil is usually a fatty oil such as a fatty acid ester, preferably a di or triester of glycerol or propylene glycol. They are well-known under such names as soy bean oil, lard oil, safflower oil, olive oil, coconut oil, Captex, etc. Preferably, it is a saturated vegetable oil. For the present purpose, it should be a C_8-C_{20}, i.e., each fatty acid chain has 8-20 carbon atoms, more preferably C_8-C_{15}. Mineral oils such as pharmaceutical or food grade white oils are also suitable and the oil can be natural or synthetic.

The amount of the fatty oil is 1-40 percent, preferably 1-20%, more preferably 2-10%. All percentages herein are volume percent, indicated as merely %, or are weight volume percent; indicated as w/v %, which is the grams per 100 ml. of emulsion. More fatty oil generally requires more emulsifier.

The aqueous phase will often contain osmotic agents such as sodium chloride and/or glycerol to maintain the osmolarity at about 300 milliosmols, the osmolarity of human blood. The use of such an agent will often depend on how much emulsion is to be injected. If being used as a drug carrier, then for some drugs, only a milliliter or so of emulsion may be necessary. This amount is small enough, compared to the total human blood volume, that no adverse effect on osmolarity may occur without an osmolarity agent being included in the emulsion. If significant quantities

of emulsion are employed, or simply as a matter of good conservative practice, such agents are desirably included in the emulsion. The same reasoning will alsoapply to the optional inclusion of buffering agents, such as phosphates, etc., to maintain blood pH.

The emulsifier used in my invention is nonionic and can be a single surfactant or a combination. At least one component of the surfactant should have a molecular weight above 2000, preferably above 2500, more preferably above 3000. As is well known the surfactant will be selected to provide an HLB to match that of the oil, the HLB being a well-known value which indicates the hydrophilicity of an emulsifier or emulsifier combination. Usually the HLB will be 10-15, preferably 11-13. As the subsequent examples show, this can often be achieved with a single surfactant. Suitable surfactants are polyoxyethylene fatty acid tri or higher esters of glycerol or sorbitol (or sorbitan). Preferably, the fatty acid is C_8-C_{30}, preferably C_{10}-C_{20}, more preferably C_{12}-C_{18}. Preferably there are about 15-60 ethylene oxide units, preferably about 20-50, more preferably about 30-40. As is well known, this number refers to the aggregate number of C_2H_4O units which are introduced at the available alcohol and ester positions in the fatty acid ester. If this number is 15-60, for example, it is generally written as "n = 15-60" or as "polyoxyethylene 15-60". Typical materials available commercially are Emulphor, Cremophor, Tween, Cirrasol and the like.

A second emulsifier component is sometimes helpful such as a fatty acid mono or diesters of glycerol or sorbitol (or sorbitan) such as Spans which may as well contain polyoxyethylene groups, the fatty acid and polyoxyethylene being as described above.

The amount of surfactant will generally be 2-40%, preferably 2-30%, more preferably 5-20%. Usually the surfactant:oil ratio is from .2:1 to 2:1.

My emulsions usually have average particle size of 10-80 nanometers, preferably 30-70, by laser light scattering. Usually there are no particles larger than 120 nanometers. They have a critical temperature range from at least as low as 40°C. up to about 500°C., i.e., they retain their microemulsion character over this range. This wide range is a singular achievement in medical emulsion technology.

The microemulsions of my invention are prepared in a certain manner. It is not sufficient to merely add all the ingredients together and thoroughly mix them. Rather, two mixtures, each containing some of the ingredients are separately prepared and then mixed together in a certain procedure.

One mixture contains the oil and high molecular weight surfactant. Preferably, it also contains any other surfactant and other oily ingredients but to achieve a microemulsion as a final product, the surfactant must be mixed with the fatty oil before being mixed with the water. If mixed with the water, the final emulsion is cloudy, has larger particle size and is not as stable. Accordingly the high molecular weight surfactant and the oil are heated to, say, 50°C. to dissolve the surfactant in the oil. The aqueous and oil phases are then mixed together to form a coarse emulsion. The emulsion is referred to as coarse in that it is the kind of emulsion one gets by hand shaking of two immiscible liquids, but it has relatively low stability and either a large average particle size and/or a wide particle size distribution. It is often milky and often has a significant number of particles above one micron.

This emulsion is then brought to or heated at above the phase inversion temperature. This is the temperature at which the emulsion, albeit coarse, breaks into two distinct liquid phases. This temperature varies for different compositions but is usually 25-150°C., preferably 65-120°C. Time is also a factor as the "breaking" will often still occur at a lower temperature if

a longer time is provided. The time required for the emulsion to break, once it is above the PIT varies but is usually only a matter of several minutes, such as 2-10 minutes, almost always within 3-60 minutes. The difference between the coarse emulsion and the "broken" two-phase system is very striking and readily visible.

It is also sometimes possible to form the coarse emulsion above the PIT, since the time required to break the emulsion once the PIT is reached is usually a few minutes, the oil and aqueous phases can be initially mixed at, say, 95°C., for an 85°C. PIT, and then held at 95°C. until the coarse emulsion breaks.

Once the emulsion has broken, it is then cooled with gentle mixing or shaking to room temperature (25°C.). At about 40-60°C. the microemulsion forms, as is generally evidenced by the appearance of a translucent, shiny blue-yellow single phase.

If the PIT is rather low, say 25-40°C., the process of the invention is still applicable, but the formation of the microemulsion will be at a lower temperature. Thus if the coarse emulsion is formed at room temperature and then breaks at 35°C., then the microemulsion may not form until 5-10°C.

As noted, the aqueous phase can also contain water-soluble excipients such as sugars, mineral salts, flavoring agents, preservatives, etc. These can be added to the aqueous phase in its initial preparation or to the finished emulsion.

A principal utility of my emulsions is as a lipophilic or amphipathic drug carrier. The drugs are included in the oil phase, although there is also some distribution or partition, usually not more than 25%, preferably not more than 5%, of the drug between the oil and water phases. The drugs I usually use are either sufficiently lipophilic inherently, or they are made so by adjustments in emulsion pH, but the subsequent examples show that they do not have to be lipophilic.

Examples of lipophilic drugs which can be used are described in European Patent 0211258. They include general anesthetics, local anesthetics, hypnotics, sedatives and anxiolytics, antidepressants, anticonvulsants, narcotic analgesics and narcotic antagonists, nonsteroidal antiinflammatory drugs, anticholinesterases, sympathomimetics and parasympathomimetics, ganglionic stimulating and blocking agents, neuromuscular blocking agents, antimuscarinic agents, adrenergic blocking agents, autacoids and autacoid antagonists, digitalis and digitalis congeners, diuretics and saliuretics, antibiotics and antimicrobials, antineoplastics, immunosuppressants and immunomodulators, hemoglobin and hemoglobin derivatives and polymers, hormones and hormone antagonists, and fat-soluble vitamins, and combinations thereof. Specific drugs within these groups are specifically identified in the aforementioned patent which is incorporated herein by reference.

The drugs can be added to the finished emulsion or to the oil phase in its preparation. Preferably, they are added to the furnished emulsion if the drugs are not resistant to the heat sometimes used in sterilizing the emulsion.

The emulsions of my invention can be sterilized by conventional autoclaving which usually involves heating at about 120°C. Alternatively, they can be sterilized by microfiltration. When heat sterilized, the emulsion will invariably break into two phases, but the single phase microemulsion will return at about 40-60°C. on gentle shaking.

Autoclaving for sterilization purposes is preferably done before any drugs are included in the emulsion for the heat resistance considerations mentioned above. If sterilized by filtration, thermal decomposition of the drug is obviously not a problem.

The following examples illustrate my invention more specifically:

EXAMPLE 1

Ethiodol (an imaging agent) , an iodinated poppyseed oil (C_{18}), is used as the oil phase and is mixed 1:1 with Cremophor EL (ethoxylated castor oil, POE = 35, mol. wt. = 2514) at room temperature until homogeneous. The oil phase is 5%. The aqueous phase (PBS) is added and the system is shaken vigorously to form a coarse emulsion. The emulsion is heated to 90-95°C. to cause phase separation and is then cooled to room temperature with gentle mixing. A microemulsion forms at and has a particle size of 30 nm.

EXAMPLE 2

The procedure is the same as in Example 1 except that the oil phase is 12%. The results are the same.

EXAMPLE 3

The procedure is the same as in Example 1 except that the oil phase is 24% and the Ethiodol:Cremophor ratio is 1.5:1. The results are the same in that a microemulsion forms but the particle size is somewhat larger because of the lesser amount of surfactant.

EXAMPLE 4

3% (w/v) Ibuprofen, 7.5% Captex 200 (C_8-C_{10} fatty acid diester of propylene glycol) and 7.2% Cremophor EL (same as Example 1) are mixed together with heating to dissolve the Ibuprofen in the oil. The aqueous phase is added and mixed to form a crude emulsion. The entire mixture is heated to 90-95°C. to cause phase separation, and is then cooled with mixing to room temperature which causes the microemulsion to form with a particle size of 65 nm. The addition of sucrose to the aqueous phase (up to 20 w/v %) causes the microemulsion particle size to be even smaller. Also, citric acid can be added to reduce the pH so that sodium benzoate, a standard preservative (0.1%) can be added to prevent bacterial contamination.

EXAMPLE 5

.041 g. of insulin is dispersed in a 1:1 mixture of coconut oil and polyoxyethylene sorbitan hexaoleate. This dispersing is by homogenization because insulin is not soluble in the oil (nor in the aqueous phase at high pH). The oil phase is 5%. The aqueous phase (PBS) is added at room temperature and mixed to form a coarse emulsion. This emulsion is heated to 90-95°C. until two distinct phases are seen, then is gently mixed while cooling to room temperature. A microemulsion forms which has a particle size of 35 nanometers. After several days the insulin starts to slowly come out of the oil phase which is not unexpected.

EXAMPLE 6

.006 g. Piroxicam (another antiinflammatory drug) is dissolved in .39 ml. Cremophor EL (Example 1), .27 ml. triacetin and .12 ml. Captex 200 (Example 1). The triacetin (acetic acid ester of glycerol) helps solubilize the drug in the oil. Dissolution is by heating at 95°C. until the white drug powder dissolved in the oil-surfactant system leaving a clear yellow solution. The aqueous phase, 2.34 ml. citric acid buffer (pH 2.3) at room temperature, was added to the oil phase which was still in the oil bath. This dropped the temperature substantially and the system stood in the bath until the emulsion broke. The emulsion vial was then removed from the bath and cooled to room temperature with gentle mixing. When it first becomes transparent, at 40-50°C., it is immersed in a room temperature water bath to accelerate cooling. The particle size of the finished emulsion is about 25 nm.

EXAMPLE 7

This Example is the preparation of a microemulsion of 5.0% lauric oil with 3.5% polyoxyethylene 50 sorbitol hexaoleate as the main surfactant and 1.0% polyoxyethylene 20 sorbitan monolaurate and 0.55 w/v% egg

yolk phospholipid (EYP) as secondary surfactants. The oil phase also contained 0.005 w/v% potassium oleate as an anticoalescing agent. The aqueous phase was phosphate buffered saline solution (10 mmoles/1 PO_4 , 300 mosmoles).

The aqueous phase is heated to 85°C. All other ingredients were mixed together and heated to 85°C. Heating is in a water bath. The two portions were then mixed together and held 85°C. for a few minutes until the crude emulsion broke and were then allowed to cool to room temperature with gentle shaking. At about 60°C. in the cooling cycle the microemulsion forms. It is a transparent single phase with a shiny blue-yellow cast. It has a stability range of at least 4-50°C. The particle size is 30 nanometers which is still the same after ten months storage.

EXAMPLE 8

The procedure is the same as in Example 7 except that the aqueous phase is 0.9 wt % NaCl solution. The pH of the finished microemulsion is adjusted from 2 to 10 with NaOH and HCl. There was no damage to the emulsion.

The invention claimed is:

1. In a process in which an oil is emulsified in water with non-ionic surfactant having a molecular weight above 2000, the improvement which comprises forming a coarse emulsion of the oil containing the surfactant, in water, heating the coarse emulsion at above the phase inversion temperature to cause the coarse emulsion to break into two phases, and cooling said broken emulsion with agitation to form a microemulsion.

2. Process according to Claim 1 wherein said phase inversion temperature is at least 65°C.

3. Process according to Claim 1 wherein said cooling is to at least 25°C.

4. Process according to Claim 1 wherein said oil is a fatty oil.

5. Process according to Claim 1 wherein said fatty oil is a triglyceride or a propylene glycol fatty acid diester.

6. Process according to Claim 1 wherein the oil phase of the microemulsion contains a drug.

7. Process according to Claim 1 wherein said surfactant is a polyoxyethylene fatty acid tri or higher ester of glycerol, sorbitol, or sorbitan.

8. In a process for forming a microemulsion by dispersing a fatty oil in an aqueous phase in the presence of fatty acid ester surfactant having a molecular weight greater than 2000, the improvement which comprises heating the fatty oil and surfactant to at least 50°C. before adding the aqueous phase thereto.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US91/03991

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): B01J 13/06

U.S. CL. 264/4.1

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	264/4.1; 424/59, 450, 451; 514/937, 938, 939, 941, 943

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X	US, A, 4,847,072 (BISSETT) 11 JULY 1989; See column 7, line 20 to column 8, line 35; column 31, line 27.	1-8
A	US, A, 4,857,335 (BOHM) 15 AUGUST 1989; See entire document.	1-8

* Special categories of cited documents: [15]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
10 SEPTEMBER 1991	03 OCT 1991
International Searching Authority [1]	**Signature of Authorized Officer [20]**
ISA/US	Gollamudi S. Kishore